

WHAT IS CLAIMED IS:

1. An isolated nucleic acid encoding a polypeptide comprising an alpha subunit of a cation channel, the polypeptide:

(i) forming, with at least one additional HAC alpha subunit, a cation channel having the characteristic of activation upon hyperpolarization; and

(ii) having an amino acid sequence that has greater than 75% identity to amino acids 1-50 of SEQ ID NO:1 or greater than 90% identity to amino acids 640-775 of SEQ ID NO:1.

2. The nucleic acid of claim 1, wherein the polypeptide specifically binds to antibodies generated against SEQ ID NO:1.

3. The isolated nucleic acid of claim 1, wherein the nucleic acid encodes an amino acid sequence of SEQ ID NO:1.

4. The isolated nucleic acid sequence of claim 1, wherein the nucleic acid has a nucleotide sequence of SEQ ID NO:2

5. The isolated nucleic acid of claim 1, wherein the nucleic acid is a splice variant of SEQ ID NO:2.

6. The isolated nucleic acid of claim 1, wherein the nucleic acid is amplified by primers that selectively hybridize under stringent hybridization conditions to the same sequence as any two primers selected from the group consisting of:

CAGCCATGGAGGCAGAGCAGCGGC (SEQ ID NO:3),

GGAGGAGATCTTTCACATGACATACGAC (SEQ ID NO:4)

AGTAGGATCCATCGGTGAGGCGTG (SEQ ID NO:5),

TTACATGTTGGCAGAAAGCTGGAGACC (SEQ ID NO:6).

7. The isolated nucleic acid of claim 1, wherein the nucleic acid encodes a polypeptide having a molecular weight of between about 85 kDa to about 95 kDa.

8. The isolated nucleic acid of claim 1, wherein the polypeptide comprises an alpha subunit of a homomeric cation channel.

9. The isolated nucleic acid of claim 1, wherein the polypeptide comprises an alpha subunit of a heteromeric cation channel.

5 10. The isolated nucleic acid of claim 1, wherein said nucleic acid selectively hybridizes under moderately stringent hybridization conditions to a nucleotide sequence of SEQ ID NO:2.

11. The isolated nucleic acid of claim 1, wherein the nucleic acid has a nucleotide sequence that has greater than 90% identity to SEQ ID NO:2.

10 12. The isolated nucleic acid of claim 1, wherein the nucleic acid encodes a polypeptide having an amino acid sequence that has greater than 96% identity to SEQ ID NO:1.

13. An isolated polypeptide comprising an alpha subunit of a cation channel, the polypeptide:

15 (i) forming, with at least one additional HAC alpha subunit, a cation channel having the characteristic of activation upon hyperpolarization; and

(ii) having an amino acid sequence that has greater than 75% identity to amino acids 1-50 of SEQ ID NO:1 or greater than 90% identity to amino acids 640-775 of SEQ ID NO:1.

20 14. The isolated polypeptide of claim 13, wherein the polypeptide specifically binds to antibodies generated against SEQ ID NO:1.

15. The isolated polypeptide of claim 13, wherein the polypeptide has an amino acid sequence of SEQ ID NO:1.

25 16. The isolated polypeptide of claim 13, wherein the polypeptide comprises an alpha subunit of a homomeric cation channel.

09767697 26529260

Sub B1

13

17. The isolated polypeptide of claim 13, wherein the polypeptide comprises an alpha subunit of a heteromeric cation channel.

18. The isolated polypeptide of claim 13, wherein the polypeptide has a molecular weight between about 85 kDa to about 95 kDa.

19. The isolated polypeptide of claim 13, wherein the polypeptide has an amino acid sequence that is greater than 96% identity to SEQ ID NO:1.

20. An antibody that selectively binds to a polypeptide of claim 13.

21. An antibody of claim 20, wherein the polypeptide has an amino acid sequence of SEQ ID NO:1.

22. An expression vector comprising the nucleic acid of claim 1.

23. A host cell transfected with the vector of claim 22.

24. A method for identifying a compound that decreases or increases ion flux through a hyperpolarization-activated cation channel, the method comprising the steps of:

(i) contacting the compound with a HAC polypeptide, the polypeptide:

(a) forming, with at least one additional HAC alpha subunit, a cation channel having the characteristic of activation upon hyperpolarization; and

(b) having an amino acid sequence that has greater than 75% identity to amino acids 1-50 of SEQ ID NO:1 or greater than 90% identity to amino acids 640-775 of SEQ ID NO:1; and

(ii) determining the functional effect of the compound upon the cation channel.

25. The method of claim 24, wherein the functional effect is a physical effect.

26. The method of claim 24, wherein the functional effect is a chemical effect.

27. The method of claim 24, wherein the polypeptide is expressed in a eukaryotic host cell or cell membrane.

28. The method of claim 27, wherein the functional effect is determined by measuring ion flux, changes in ion concentration, changes in current, changes in voltage, or changes in yeast viability on low potassium medium.

29. The method of claim 24, wherein the functional effect is determined by measuring ligand binding to the channel.

30. The method of claim 24, wherein the polypeptide is recombinant.

31. The method of claim 24, wherein the cation channel is homomeric.

32. The method of claim 24, wherein the cation channel is heteromeric.

33. The method of claim 24, wherein the polypeptide has an amino acid sequence of SEQ ID NO:1.

34. A method for identifying a compound that increases or decreases ion flux through a HAC potassium channel comprising a human HAC polypeptide, the method comprising the steps of:

(i) entering into a computer system an amino acid sequence of at least 50 acids of a human HAC polypeptide or at least 150 nucleotides of a nucleic acid encoding the human HAC polypeptide, the human HAC polypeptide having an amino acid sequence that has greater than about 75% identity to amino acids 1-50 of SEQ ID NO:1 or greater than 90% identity to amino acids 640-775 of SEQ ID NO:1;

(ii) generating a three-dimensional structure of the polypeptide encoded by the amino acid sequence;

(iii) generating a three-dimensional structure of the potassium channel comprising the human HAC polypeptide;

(iv) generating a three-dimensional structure of the compound; and

(v) comparing the three-dimensional structures of the polypeptide and the compound to determine whether or not the compound binds to the polypeptide.

35. A method of modulating ion flux through a human HAC channel, the method comprising the step of contacting the human HAC channel with a or claim 34.

36. A method of detecting the presence of human HAC3 in a sample, the method comprising the steps of:

- (i) isolating a biological sample;
- (ii) contacting the biological sample with a human HAC3-specific reagent that selectively associates with human HAC3; and,
- (iii) detecting the level of human HAC3-specific reagent that selectively associates with the sample.

37. The method of claim 36, wherein the human HAC3-specific reagent is selected from the group consisting of: human HAC3 specific antibodies, human HAC3 specific oligonucleotide primers, and human HAC3 nucleic acid probes.

38. In a computer system, a method of screening for mutations of human HAC3 genes, the method comprising the steps of:

- (i) entering into the computer system a first nucleic acid sequence encoding a HAC cation channel polypeptide having a nucleotide sequence of SEQ ID NO:2, and conservatively modified versions thereof;
- (ii) comparing the first nucleic acid sequence with a second nucleic acid sequence having substantial identity to the first nucleic acid sequence; and
- (iii) identifying nucleotide differences between the first and second nucleic acid sequences.

39. The method of claim 38, wherein the second nucleic acid sequence is associated with a disease state.